Is Pancreatic Diabetes (Type 3c Diabetes) Underdiagnosed and Misdiagnosed?

PHILIP D. HARDT, MD, PHD
MATHIAS D. BRENDEL, MD
HANS U. KLOER, MD, PHD
REINHARD G. BRETZEL, MD, PHD

Exocrine pancreatic insufficiency is frequently associated with diabetes, with high prevalence in both insulin-dependent or insulin-independent patients. Exocrine pancreatic failure has often been perceived as a complication of diabetes. In contrast, recent clinical observations lead to the notion that nonendocrine pancreatic disease is a critical factor for development rather than a sequel to diabetes. The incidence of diabetes caused by exocrine pancreatic disease appears to be underestimated and may comprise 8% or more of the general diabetic patient population. Nonendocrine pancreas disease can cause diabetes by multiple mechanisms. Genetic defects have been characterized, resulting in a syndrome of both exocrine and endocrine failure. Regulation of β-cell mass and physiological incretin secretion are directly dependent on normal exocrine function. Algorithms for diagnosis and therapy of diabetes should therefore address both endocrine and exocrine pancreatic function.

Diabetes Care 31 (Suppl. 2):S165–S169, 2008

Several pancreatic diseases have been reported as causes of diabetes, with a low incidence of ~0.5–1.15% among all cases of diabetes (1,2). In contrast, exocrine pancreas dysfunction in patients with diabetes has been estimated to be present in up to 50% of subjects in retrospective historical observations in studies with small numbers of patients (3–5). At that time, only invasive diagnostic procedures were available, thus preventing widespread assessment of exocrine pancreas function in patients with diabetes.

Various hypotheses have been put forward to explain the frequent finding of exocrine insufficiency in diabetes: first, dysregulation of exocrine secretion due to diabetic neuropathy (6) and atrophy of exocrine tissue due to lack of local trophic insulin effects (7) or related to local or general vascular damage; second, simultaneous exocrine and endocrine dysfunction as a net result of a common underlying process affecting the whole pancreas, and autoimmune-mediated inflammation induced by the presentation of both β-cell–specific and exocrine tissue antigens (8,9) and genetic defects of exocrine and endocrine cells (10), possibly triggered by previous viral or bacterial infection; and third, a higher prevalence of pancreatic disease with exocrine dysfunction (5) as a cause for diabetes (type 3c in current classifications [11]).

PREVALENCE OF PANCREATIC EXOCRINE INSUFFICIENCY IN PATIENTS WITH DIABETES

— In recent years, the evaluation of exocrine pancreatic function has been greatly facilitated by newly available noninvasive stool tests allowing screening of large patient populations. Measurement of fecal elastase-1 concentrations (FECs) by enzyme-linked immunosorbent assay based on monoclonal human specific antibodies has become a standard diagnostic parameter with good correlation to direct tests of pancreatic exocrine function (12) and morphological pancreas alterations (13), albeit limited sensitivity in mild pancreatic exocrine insufficiency.

Exocrine pancreatic function using FEC assessment has been extensively studied in patients with diabetes. Normal exocrine function (FEC >200 μg/g) was observed in ~58% of patients with diabetes (n = 2,001), while pancreatic exocrine insufficiency (pancreatic exocrine insufficiency; FEC <100 μg/g) occurred in 12–20% of patients without insulin therapy, in most cases classified as "type 2," and in 26–44% of patients on subcutaneous insulin therapy, in the majority of cases classified as "type 1" (Table 1) (14–19).

The overall prevalence of ~42% for impaired exocrine pancreatic function in patients with diabetes reported in these studies is in line with previous findings using direct tests of pancreas exocrine function.

MORPHOLOGIC CHANGES OF THE EXOCRINE PANCREAS IN PATIENTS WITH DIABETES

— It has been noted that alterations of exocrine pancreatic morphology frequently occur in patients with diabetes. Examinations comprise autopsy studies on macroscopic and histological changes (20–22), ultrasound and computed tomography morphology (23), and imaging of the pancreatic duct system by endoscopic retrograde pancreaticography (24,25). Pathological pancreatic ducts characteristic for chronic pancreatitis (according to the Cambridge classification) have been observed in ~35% of patients previously diagnosed as having type 2 diabetes and up to 50% of patients previously diagnosed as having type 1 diabetes.

Taken together, ~40% of all patients with diabetes show alterations of exocrine pancreatic morphology as well as of exocrine function characteristic for chronic pancreatitis.

PREVALENCE OF PANCREATIC DIABETES: THE RECLASSIFICATION STUDY

— The frequent association of exocrine and endocrine pancreas disease is consistent with an increased prevalence of pancreatic diabetes (type 3c). In light of this observation, we recently reclassified all patients with diabetes treated at our hospital during a 1-year period (Ewald N, Kaufmann C, Raspe A, Kloer HU, Bretzel

From the Third Medical Department and Policlinic, University Hospital Giessen and Marburg, Giessen, Germany.

Address correspondence and reprint requests to Philip D. Hardt, Third Medical Department and Policlinic, University Hospital Giessen and Marburg, Giessen, Rodthohl 6, D-35385 Giessen, Germany. E-mail: philip.d.hardt@innere.med.uni-giessen.de.

The authors of this article have no relevant duality of interest to declare.

This article is based on a presentation at the 1st World Congress of Controversies in Diabetes, Obesity and Hypertension (CODHy). The Congress and the publication of this article were made possible by unrestricted educational grants from MSD, Roche, sanofi-aventis, Novo Nordisk, Medtronic, LifeScan, World Wide, Eli Lilly, Keryx, Abbott, Novartis, Pfizer, Generx Biotechnology, Schering, and Johnson & Johnson.

Abbreviations: FEC, fecal elastase-1 concentration; GLP, glucagon-like peptide.

DOI: 10.2337/dc08-s244

Table 1—*Prevalence of exocrine pancreatic insufficiency as determined by FEC*

	Diabetes type	Number of subjects	Normal function (FEC >200 μg/g) (%)	Insufficiency (FEC <100 μg/g) (%)
Study	1			
Hardt et al. (14)		39	36	44
Hardt et al. (14)	2	77	64	20
Rathmann et al. (15)	2	544	—	11.9
Icks et al. (16)	1	112	—	25.9
Nunes et al. (17)	—	42	64	—
Hardt et al. (18)	1 + 2	1,015	59.3	22.9
Mancilla et al. (19)	1 + 2	72	67	19
Sum/mean	1 + 2	2,001	58	27

RG, Hardt PD, unpublished data), based on standard classification criteria: type 1 diabetes: presence of autoantibodies, early onset, immediate insulin requirement; type 2 diabetes: absence of autoantibodies, no (or late) insulin requirement, insulin resistance; type 3 diabetes: absence of autoantibodies, and both exocrine pancreatic insufficiency and typical morphologic pathology.

Clinical records of 1,922 patients were retrospectively examined for these criteria. Of these, 157 (8%) were reclassified as diabetes type 3c, 227 (12%) as type 1 diabetes, and 1,538 (80%) as type 2 diabetes.

Distribution of exocrine pancreas disease in this population included chronic pancreatitis (76%), hemochromatosis (8%), pancreatic cancer (9%), cystic fibrosis (4%), and previous pancreatic surgery (3%), which is in accordance with other publications.

The rate of 8% of type 3c diabetes might be underestimated, since FEC tests were available for only 307 of the 1,992 total patients, and both pancreas exocrine insufficiency and morphological alterations were seen in 157 of these 307. It is very likely that additional cases of type 3c diabetes are present in the remaining 1,685 patients, further increasing the true prevalence. If confirmed in prospective studies, this observation would significantly change the current notion of diabetes epidemiology.

HOW CAN TYPE 3C DIABETES BE FREQUENT IF PANCREATIC DISEASES ARE UNCOMMON?

— One main argument against the assumption that type 3c diabetes is a frequent problem is the general belief that diseases of the exocrine pancreas are rather scarce. Clinical studies report an incidence of only 0.2–8 in 1,000 people per year for chronic pancreatitis (27). In contrast, several autopsy studies report a prevalence of chronic pancreatitis in 5.3–13% of 394 and 3,821 people, respectively, in selected autopsies (28,29). Interestingly, the clinical diagnosis of chronic pancreatitis had been made in only a minority of those patients (0.5%), and the prevalence of chronic pancreatitis was much higher in patients with known diabetes (11.2–19%) compared with 5.3–7% in nondiabetic patients. These data underscore a significant underestimation of chronic pancreatitis in current medical practice. This might in part be explained by the fact that diagnostic tools have been invasive in the past and have therefore been restricted to a small patient population. Furthermore, clinical symptoms of chronic pancreatitis are unspecific, particularly in an early stage of the disease. We initiated the first population-based study reporting pancreatic insufficiency in 11.5% (914 subjects, age 50–75 years) (30). This number is in accordance with observations from the autopsy studies cited above.

PANCREAS DEVELOPMENT: TRANSDUCTION AND TRANSDIFFERENTIATION OF ISLET CELLS

— It has been shown that the β-cell mass is not a fixed cell population, but is subject to a permanent reconstitution (31). Increase in β-cell mass can occur through various mechanisms: *1*) increased β-cell replication, *2*) β-cell size increase, *3*) reduced β-cell death rate, and *4*) differentiation from β-cell precursor cells. There is evidence that islet cell formation can originate from ductal epithelial tissue. β-Cell neogenesis from a pancreatic precursor cell pool was found in several models of experimental pancreas lesions (32). In addition, data from animal models suggest transdifferentiation of β-cells from precursor ductal cells. Moreover, soluble growth and regeneration factors (e.g., islet neogenesis-associated protein [INGAP], gastrin, and epithelial growth factor [EGF]) have been shown to (trans)-differentiate β-cells from acinar and ductal pancreatic cells in rodents and humans. Rat and human ductal epithelial cells, possibly containing endocrine pancreatic precursor cells, proliferate and transdifferentiate under specific culture conditions in vitro (33). Similarly, transduction of endocrine transcription factors for β-cell development (e.g., Ngn-3, PDX-1) can drive ductal cells toward β-cell phenotypes (34). Currently, transdifferentiation cannot be dissected from propagation and differentiation of precursors versus dedifferentiation or "lineage switching" from differentiated nonendocrine pancreas cells. However, in light of the association between pancreas exocrine and endocrine deficiency, the concept of "shared injury" and common origin of exocrine and endocrine pancreatic precursor cells deserves greater attention.

DIABETES AND PANCREATIC EXOCRINE DYSFUNCTION DUE TO MUTATIONS IN THE CARBOXYL-ESTER LIPASE

— It has been speculated for several years that genetic factors might contribute to exocrine dysfunction in diabetes. Only recently, a relevant mutation has been uncovered in two Norwegian families with diabetes and exocrine pancreas dysfunction (10). Affected members of this family presented with a type of diabetes characterized by primary β-cell failure and simultaneous pancreatic exocrine dysfunction. Genomic screening has linked diabetes to chromosome 9q34. Using fecal elastase deficiency as a marker of pancreatic exocrine dysfunction further refined the critical chromosomal region to 1.16 Mb. A heterozygous frame-shift mutation was identified in exon 11 of the carboxyl-ester lipase (CEL) gene. This enzyme is a major component of pancreatic juice and is responsible for the duodenal hydrolysis of cholesterol esters and other complex lipids. The in vitro catalytic activities of wild-type and mutant carboxyl-ester lipases were similar. In contrast, the mutant enzyme was significantly less stable compared with wild-type CEL. A

polygenic role for this region is likely, since common insertions were associated with exocrine dysfunction in other diabetic patients. To further explore early pathological events in this condition, radiological examinations of the pancreas were performed in nondiabetic children carrying genetic mutations with signs of exocrine dysfunction. Development of diabetes was preceded by pancreas lipomatosis. These findings link diabetes to the disrupted function of a lipase in the pancreatic acinar cells and imply that fatty replacement of the normal pancreas structure contributes to development of pancreatic disease development. A number of studies have been initiated to further investigate the quantitative relevance of this genetic mutation.

THE ROLE OF INCRETIN HORMONES

— The gut hormones glucose-dependent insulinotrophic polypeptide (GIP) and glucagon-like peptide (GLP)-1 are secreted in response to nutrient digestion and absorption. GIP is known to stimulate insulin secretion and to retard gastric emptying. GLP-1 stimulates insulin and suppresses glucagon secretion, reduces appetite, and likewise decelerates gastric emptying (35,36). Furthermore, it was shown to stimulate β-cell neogenesis, growth, and differentiation in rodents and tissue culture and to inhibit β-cell apoptosis in vitro. GLP-1 can normalize plasma glucose levels in type 2 diabetes. The hormone is rapidly inactivated by proteolysis (dipeptidyl peptidase IV [DPP IV]) and eliminated through the kidney. Therefore, agents interacting with GLP-1 receptors either found in nature or developed by intentional modification of GLP-1 as "incretin mimetics" have been developed as antidiabetic agents (37). It is currently unclear whether long-term use of such agents will prevent or slow down the continuous decline in β-cell function and mass associated with progression of type 2 diabetes. Animal experiments show an increase in β-cell mass within weeks of treatment with dipeptidyl peptidase IV inhibitors and enhanced β-cell preservation (38).

CLINICAL CONSEQUENCES OF EXOCRINE PANCREATIC INSUFFICIENCY IN PATIENTS WITH DIABETES

— Chronic pancreatitis without major clinical symptoms is present in a high percentage of patients with diabetes. Contrary to common belief, that chronic pancreatitis in these patients is generally alcohol induced, we suggest other critical factors be considered, such as genetic changes (10), autoimmunity toward exocrine antigens (8,9), and chronic inflammation associated with gallstone disease and consequent obstructive pancreatitis (39,40). There is clearly a lack of prospective studies to characterize the pathophysiological relevance of these conditions. To prevent progression of chronic pancreatitis to overt exocrine and endocrine function, screening programs to detect pancreas disease at an early stage should be considered.

Patients with diabetes and pancreatic exocrine insufficiency as measured by FEC develop overt steatorrhea in ~60% of the cases (41). Even in patients considered to have normal exocrine function by FEC, steatorrhea can sometimes be present (42). Fecal fat excretion is of high relevance for clinical symptoms (meteorism, abdominal pain, diarrhea) and qualitative or even quantitative malnutrition (e.g., deficiency of fat-soluble vitamins).

In patients with diabetes and pancreatic exocrine insufficiency, meteorism and stool texture correlate with steatorrhea, whereas abdominal pain and stool frequency do not. In an intervention study using exocrine pancreatic enzyme replacement therapy, steatorrhea was reverted, while no statistically significant effect on gastrointestinal symptoms was detected (Hardt PD, Hauenchild A, Jaeger C, Teichmann J, Bretzel RG, Kloer HU, unpublished data).

To date, there is only limited information available on the impact of chronic pancreatitis on qualitative malnutrition. High rates of exocrine pancreas dysfunction have been reported in patients with osteoporosis and vitamin D deficiency (43). However, in another study in diabetic patients with reduced FEC, levels of fat-soluble vitamins remained within normal levels during a 16-week follow-up in both enzyme replacement and placebo group (43a).

The influence of pancreas enzyme replacement therapy on glucose metabolism in insulin-treated patients with exocrine insufficiency remains controversial. Whereas improved blood glucose control and reduced A1C were reported in one study (44), others found no effect (45,46).

In addition, chronic pancreatitis and exocrine dysfunction have been associated with impairments of the incretin system. It has been previously demonstrated that glucose-dependent insulinotrophic polypeptide secretion is reduced in patients with steatorrhea due to alcoholic pancreatitis and can be normalized by enzyme replacement therapy (47). To our knowledge, no studies have been performed on the effect of exocrine pancreas enzyme substitution on incretin function in patients with chronic pancreatitis and type 3c diabetes.

CONCLUSIONS

— Pancreatic exocrine insufficiency, as determined by both direct and indirect function tests, is very frequent in patients with diabetes and is often associated with steatorrhea. It not only affects patients with type 1 diabetes (up to 50%), but is also observed in type 2 diabetic patients. In addition to impaired exocrine function, pancreatic morphological changes are present in up to 40% of the cases. Several hypotheses have been generated to interpret these findings and are consistent with the explanation that type 3c diabetes is indeed more common than previously believed. It might affect at least 8% of all patients with diabetes. Of particular interest is the presence of genetic mutations that can induce both exocrine and endocrine failure, which has recently been demonstrated for the CEL gene. Furthermore, it has been suggested that β-cell regeneration is disturbed in pancreatic diseases, which could explain reduced β-cell mass and diabetes in chronic pancreatitis. Incretin secretion is impaired in steatorrhea, since the extent of incretin secretion depends on regular digestion of nutrients. The implications of the above-described findings deserve more attention, since they are likely to change the clinical workup of patients with diabetes or impaired glucose tolerance and could change the current paradigm of diabetes epidemiology. Diagnostic and screening strategies must be adapted to detect exocrine diseases at earlier stages and possibly to stop progression to overt exocrine and endocrine pancreas insufficiency. In patients with steatorrhea, pancreatic enzyme replacement therapy is warranted for treating symptoms and preventing qualitative malnutrition. Furthermore, it seems very likely that pancreatic enzyme replacement therapy will augment incretin secretion and thus become a valuable treatment modality.

Acknowledgments— This article is a summary of the controversy session at the First

Congress on Controversies in Obesity, Diabetes and Hypertension (CODHy), 26–29 October 2006, Berlin, Germany.

References

1. Alberti KGMM: An example of brittle diabetes. In *Diabetes Secondary to Pancreatopathy: International Congress Series 762.* Tiengo A, Alberti KGMM, DelPrato S, Vranic M, Eds. Amsterdam, the Netherlands, Excerpta Medica, 1988, p. 7–20
2. Günther O: *Zur Ätiologie des Diabetes mellitus.* Akademie-Verlag, Berlin, Germany, 1961
3. Pollard H, Miller L, Brewer W: External secretion of the pancreas and diabetes (study of secretin test). *Am J Dig Dis* 10: 20, 1943
4. Vacca JB, Henke WJ, Knight WA: The exocrine pancreas in diabetes mellitus. *Ann Intern Med* 61:242–247, 1964
5. Chey WY, Shay H, Shuman CR: External pancreatic secretion in diabetes mellitus. *Ann Intern Med* 59:812–821, 1963
6. Pirart J: Diabetes mellitus and its degenerative complications: a prospective study of 4.400 patients observed between 1947 and 1973. *Diabetes Care* 1:252, 1978
7. Adler G, Kern HF: Regulation of exocrine pancreatic secretory process by insulin. *Horm Metab Res* 7:290–296, 1975
8. Taniguchi T, Okazaki K, Okamoto M, Seko Shuji, Tanaka J, Uchida K, Nagashima K, Kurose T, Yamada Y, Chiba T, Seino Y: High prevalence of autoantibodies against carbonic anhydrase II and lactoferrin in type 1 diabetes: concept of autoimmune exocrinopathy and endocrinopathy of the pancreas. *Pancreas* 27:26–30, 2003
9. Kobayashi T, Nakanishi K, Kajio H, Morinaga S, Sugimoto T, Murase T, Kosaka K: Pancreatic cytokeratin: an antigen of pancreatic exocrine cell autoantibodies in type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 33:363–370, 1990
10. Raeder H, Johansson S, Holm PI, Haldorsen IS, Mas E, Sbarra V, Nermoen I, Eide SA, Grevle L, Bjorkhaug L, Sagen JV, Aksnes L, Sovik O, Lombardo D, Molven A, Njolstad PR: Mutations in the CEL VNTR cause a syndrome of diabetes and pancreatic exocrine dysfunction. *Nat Genet* 38: 54–62, 2006
11. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 21 (Suppl. 1):5–19, 1998
12. Löser C, Möllgaard A, Fölsch UR: Faecal elastase 1: a novel, highly sensitive, and specific tubeless pancreatic function test. *Gut* 39:580–586, 1996
13. Hardt PD, Marzeion AM, Schnell-Kretschmer H, Wüsten O, Nalop J, Zekorn T, Kloer HU: Fecal elastase 1 measurement compared with endoscopic retrograde cholangiopancreatography for the diagnosis of chronic pancreatitis. *Pancreas* 25:e6–e9, 2002
14. Hardt PD, Krauss A, Bretz L, Porsch-Oezcueruemez M, Schnell-Kretschmer H, Mäser E, Bretzel RG, Zekorn T, Klör HU: Pancreatic exocrine function in patients with type-1 and type-2 diabetes mellitus. *Acta Diabetologia* 37:105–110, 2000
15. Rathmann W, Haastert B, Icks A, Giani G, Hennings S, Mitchell J, Curren S, Wareham NJ: Low fecal elastase 1 concentrations in type 2 diabetes. *Scand J Gastroenterol* 36:1056–1061, 2001
16. Icks A, Haastert B, Giani G, Rathmann W: Low fecal elastase 1 in type 1 diabetes mellitus. *Z Gastroenterol* 39:823–830, 2001
17. Nunes AC, Pontes JM, Rosa A, Gomes L, Carvalheiro M, Freitas D: Screening for pancreatic exocrine insufficiency in patients with diabetes mellitus. *Am J Gastroenterol* 98:2672–2675, 2003
18. Hardt PD, Hauenschild A, Nalop J, Marzeion AM, Jaeger C, Teichmann J, Bretzel RG, Hollenhorst M, Kloer HU, S2453112/S2453113 Study Group: High prevalence of exocrine pancreatic insufficiency in diabetes mellitus: a multicenter study screening fecal elastase 1 concentration in 1,021 diabetic patients. *Pancreatology* 3:395–402, 2003
19. Mancilla AC, Hurtado HC, Tobar AE, Orellana NI, Pineda BP, Castillo MI, Ledezma RR, Berger FZ: Pancreatic exocrine function in diabetes mellitus: determination of fecal elastase. *Rev Med Chil* 134: 407–414, 2006
20. Lazarus SS, Volk BW: Pancreas in maturity-onset diabetes. *Arch Path (Chicago)* 71:44–48, 1961
21. Gepts W: Pathologic anatomie of the pancreas in juvenile diabetes. *Diabetes* 14:619–633, 1965
22. Kobayashi T, Nakanishi K, Sugimoto T, Murase T, Kosaka K: Histopathological changes of the pancreas in islet cell antibodies (ICA)-positive subjects before and after the clinical onset of insulin-dependent diabetes mellitus. *Diabetes* 37:24A, 1988
23. Gilbeau J, Poncelet V, Libon E Derue G, Heller FR: The density, contour and thickness of the pancreas in diabetics. *Am J Roentgenol* 159:527–531, 1992
24. Nakanishi K, Kobayashi T, Miyashita H, Okubo M, Sugimoto T, Murase T, Hashimoto M, Fukuchi S, Kosaka K: Exocrine pancreatic ductograms in insulin-dependent diabetes mellitus. *Am J Gastroenterol* 89:762–766, 1994
25. Hardt PD, Killinger A, Nalop J, Schnell-Kretschmer H, Zekorn T, Klör HU: Chronic pancreatitis and diabetes mellitus: a retrospective analysis of 156 ERCP investigations in patients with insulin-dependent and non-insulin-dependent diabetes mellitus. *Pancreatology* 2:30–32, 2002
27. Andersen BN, Pedersen NT, Scheel J, Woming H: Incidence of alcoholic chronic pancreatitis in Copenhagen. *Scand J Gastroenterol* 17:247–252, 1982
28. Blumenthal HT, Probstein JG, Berns AW: Interrelationship of diabetes mellitus and pancreatitis. *Arch Surg* 87:844–850, 1963
29. Olsen TS: The incidence and clinical relevance of chronic inflammation in the pancreas in autopsie material. *Acta Pathologica et Microbiologica Scandinavia, Section A* 86:361–364, 1978
30. Rothenbacher D, Low M, Hardt PD, Klor HU, Ziegler H, Brenner H: Prevalence and determinants of exocrine pancreatic insufficiency among older adults: results of a population-based study. *Scand J Gastroenterol* 40:697–704, 2005
31. Bouwens L, Rooman I: Regulation of pancreatic beta-cell mass. *Physiol Rev* 85: 1255–1270, 2005
32. Guido L, Basta G, Racanicchi L, Mancuso F, Luca G, Macchiarulo G, Brunetti P, Calafiore R: Short-term stimulation studies on neonatal pig pancreatic duct-derived cell monolayers. *Transplant Proc* 37: 2715–2718, 2005
33. Todorov I, Omori K, Pascual M, Rawson J, Nair I, Valiente L, Vuong T, Matsuda T, Orr C, Ferreri K, Smith CV, Kandeel F, Mullen Y: Generation of human islets through expansion and differentiation of non-islet pancreatic cells discarded (pancreatic discard) after islet isolation. *Pancreas* 32:130–138, 2006
34. Bretzel RG, Eckhard M, Brendel MD: Pancreatic islet and stem cell transplantation: new strategies in cell therapy of diabetes mellitus. *Panminerva Med* 46:25–42, 2004
35. Creutzfeldt W: The [pre-] history of the incretin concept. *Regul Pept* 15:87–91, 2005
36. Flatt PR, Green BD: Nutrient regulation of pancreatic beta-cell function in diabetes: problems and potential solutions. *Biochem Soc Trans* 34:774–778, 2006
37. Stonehouse AH, Holcombe JH, Kendall DM: Management of type 2 diabetes: the role of incretin mimetics. *Expert Opin Pharmacother* 7:2095–2105, 2006
38. Mu J, Woods J, Zhou YP, Roy RS, Li Z, Zycband E, Feng Y, Zhu L, Li C, Howard AD, Moller DE, Thornberry NA, Zhang BB: Chronic inhibition of dipeptidyl peptidase-4 with a sitagliptin analog reserves pancreatic β-cell mass and function in a rodent model of type 2 diabetes. *Diabetes* 55:1695–1704, 2006
39. Födisch HJ: *Feingewebliche Studien zur Orthologie und Pathologie der Papilla Vateri.* Stuttgart, Germany, Thieme Verlag, 1972
40. Hardt PD, Bretz L, Krauss A, Schnell-Kretschmer H, Wüsten O, Nalop J, Zekorn T, Kloer HU: Pathological pancre-

atic exocrine function and duct morphology in patients with cholelithiasis. *Dig Dis Sci* 46:536–539, 2001
41. Hardt PD, Hauenschild A, Jaeger C, Teichmann J, Bretzel RG, Kloer HU, S2453112/S2453113 Study Group: High prevalence of steatorrhea in 101 diabetic patients likely to suffer from exocrine pancreatic insufficiency according to low fecal elastase 1 concentrations: a prospective multicenter study. *Dig Dis Sci* 48:1688–1692, 2003
42. Cavalot F, Bonomo K, Fiora E, Bacillo E, Salacone P, Chirio M, Gaia E, Trovati M: Does pancreatic elastase-1 in stools predict steatorrhea in type 1 diabetes? *Diabetes Care* 29:719–721, 2006
43. Mann ST, Stracke H, Lange U, Klor HU, Teichmann J: Alterations of bone mineral density and bone metabolism in patients with various grades of chronic pancreatitis. *Metabolism* 52:579–585, 2003
43a. Ewald N, Bretzel RG, Fantus IG, Hollenhorst M, Kloer HU, Hardt PD: Pancreatin therapy in patients with insulin-treated diabetes mellitus and exocrine pancreatic insufficiency according to low fecal elastase 1 concentrations: results of a prospective multi-centre trial. *Diabetes Metab Res Rev* 23:386–391, 2007
44. Mohan V, Poongothai S, Pitchumoni CS: Oral pancreatic enzyme therapy in the control of diabetes mellitus in tropical calculous pancreatitis. *Int J Pancreatol* 24:19–22, 1998
45. O'Keefe SJ, Cariem AK, Levy M: The exacerbation of pancreatic endocrine dysfunction by potent pancreatic exocrine supplements in patients with chronic pancreatitis. *J Clin Gastroenterol* 32:319–323, 2001
46. Glasbrenner B, Malfertheiner P, Kerner W, Scherbaum WA, Ditschuneit H: Effect of pancreatin on diabetes mellitus in chronic pancreatitis. *Z Gastroenterol* 28: 275–279, 1990
47. Ebert R, Creutzfeldt W: Reversal of impaired GIP and insulin secretion in patients with pancreatogenic steatorrhea following enzyme substitution. *Diabetologia* 19:198–204, 1980